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Cocaine and Pregnancy

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Cocaine is a tropane alkaloid derived from cocoa plants (Zuckerman et al., 1995). Cocaine is used recreationally, either by inhalation, intravenous injection or smoking derivatives, such as crack. Maternal urine tests and self-reports suggest the prevalence of maternal cocaine use ranges from 7 to 15%, while newborn meconium screening showed a range from 4 to 31% (Holzman and Paneth, 1994), with higher prevalence, up to 62%, in women receiving no prenatal care (Spence, 1991). More recently, the NIDA data suggested that 1-2% of newborns are exposed to cocaine based on maternal report and blinded urine testing (NIDA, 1992). This Risk Newsletter will address maternal cocaine exposure and its effects on pregnancy.

Pharmacology of Cocaine

Cocaine blocks neurotransmitter reuptake, enhancing nerve stimulation by using more neurotransmitters. This increases plasma levels of norepinephrine and epinephrine, and activates adrenergic receptors. These receptors produce smooth muscle contraction and vasoconstriction in arterial beds, increasing the user's heart rate and cardiac contractility (Plessinger and Woods, 1993). Cocaine has a low molecular weight, allowing it to rapidly cross the placenta into the fetal circulatory system. Once in the body, cocaine is primarily metabolized in the liver; this results in a longer half life in the newborn due to the immaturity of the newborn's liver. It takes 5-6 days for a newborn's urine to be cleared of cocaine, versus 2 days in adults (Holzman and Paneth, 1994).

Physiological effects on the fetus

Maternal cocaine exposure may affect the fetus both directly and indirectly. As in adults, cocaine may block the reuptake of neurotransmitters in the fetus, resulting in fetal vasoconstriction, hypertension and tachycardia. Theoretically, cocaine can indirectly affect the fetus by constricting the uterine arteries, reducing placental blood flow and fetal oxygen delivery (Holzman and Paneth, 1994). In vitro experiments have also suggested that cocaine exposure increases uterine contractility.

Methodological issues

Many studies address the effects of cocaine on pregnancy. However, several methodologic issues create uncertainty in studying the effects of maternal cocaine exposure on the fetus. First, it is difficult to accurately identify users and to determine the dose and the gestational timing of exposure. Second, selection bias is likely within studies, particularly if the samples involve women in drug treatment programs or women suspected of substance use by clinical staff (Zuckerman et al., 1995). Third, failure to control for confounding factors such as polydrug use, low socioeconomic status, chaotic social environment, poor nutrition, poor prenatal care and an increased incidence of sexually transmitted

diseases (STDs) may lead to the overestimation of cocaine's effects on pregnancy (Holzman and Paneth, 1994; Zuckerman et al., 1995). Fourth, it is difficult to find control groups with similar demographic status, including cigarette and alcohol exposures. Lastly, studies that explore the long term effects of maternal cocaine exposure are rare due to high subject loss and poor follow up.

Pregnancy complications

Although the full extent of the effects of maternal cocaine exposure remain unclear, a number of risks have been reported. These include spontaneous abortion, placental abruption, preterm delivery and fetal growth retardation. Several studies suggested that poor prenatal care and polydrug exposure intensify the effects of maternal cocaine exposure.

Two studies have found that women using cocaine, either alone or with narcotics, had an increased incidence of prior spontaneous abortions compared to women using only narcotics (Chasnoff et al., 1985; Bateman, et al., 1993). Other studies have not addressed this correlation, but a meta-analysis of the available information suggested significance only when polydrug users were included in the analysis (Lutiger et al., 1991).

Numerous studies have linked maternal cocaine exposure with placenta abruptio, with reports ranging from 0 to 19% (odds ratio ranged from 1.0-9.2 with polydrug exposures). Several of these studies found increased risks only in conjunction with other drug use (Keith et al., 1989; MacGregor et al., 1989). Other studies, summarized in Holzman and Paneth (1994), have failed to find any association with placental abruption. The odds ratios associating cocaine use and placenta abruptio range greatly within studies, suggesting that confounding variables such as tobacco and alcohol exposure may impact these effects (Holzman and Paneth, 1994). A study by Ostrea et al. (1992) found that the increased risk of placenta abruptio is confined to cocaine use close to delivery. These conflicting results raise the possibility that an association between placenta abruptio and cocaine use may be dependent on dose, timing and exposure.

Several studies have found an association between cocaine use during pregnancy and preterm delivery; the odds ratio ranges from OR 1.1 to 10.6, but averages 2-3 times that of non-drug using controls (Holzman and Paneth, 1994). However, many of these studies did not control for confounding factors such as polydrug use or the incidence of sexually transmitted diseases. Preterm delivery may be related to the drug-user's lifestyle rather than a direct effect of cocaine (Holzman and Paneth, 1994).

Many large retrospective studies have associated maternal cocaine exposure with in utero growth restriction, even when gestational age is corrected for (Holzman and Paneth, 1994). Low birth weight, microcephaly and reduced fetal length have consistently been observed in cocaine exposed newborns (Zuckerman et al., 1989).

Microcephaly has commonly been reported in conjunction with decreased birth weight, indicating that the growth retarding effects of cocaine involve the whole fetus (Holzman and Paneth, 1994). This growth restriction may be due to chronic fetal hypoxia and poor delivery of nutrients to the fetus as a result of either uterine vessel constriction and/or maternal appetite suppression due to cocaine use (Holzman and Paneth, 1994).

Growth retardation appears to be confined mainly to the prenatal period. A longitudinal study regarding the growth outcomes of cocaine exposed children revealed that, with the exception of head circumference, they caught up with their non-exposed counterparts by 18 months of age (Weathers et al., 1993; Zuckerman et al., 1995).

Congenital Malformations

Unlike other drugs such as alcohol, there is no recognized entity of "fetal cocaine syndrome" and no

pattern of malformation has been consistently associated with maternal cocaine use (Zuckerman et al., 1995). Maternal cocaine exposure has been associated with the following malformations: urogenital anomalies (Chavez et al., 1989), distal limb deformities (Hoyme et al., 1990), intestinal atresia (Hoyme et al., 1988), cardiac defects (Little et al., 1989; Lipshultz et al., 1991) and central nervous system malformations (Zuckerman et al., 1995). Perhaps the observed malformations occur secondary to vasoconstriction caused by cocaine use, which disrupts the blood flow to the developing fetus. The observed malformations can occur throughout gestation (Holzman and Paneth, 1994).

Of the above associations, only urinary tract abnormalities have shown significant increases with cocaine exposure in humans and animals. This increased incidence was initially reported in a large case control study by Chavez et al. (1989). The study, involving 1067 liveborns and stillborn with urinary or genital anomalies and 3029 controls, found an association between cocaine and urinary tract malformations (OR 4.39; 95% C.I. 1.12-17.24). No statistically significant association was found with genital defects. Similar findings were seen in one other study (Chasnoff et al., 1988), and in a meta-analysis (Lutiger et al., 1991).

Distal limb reduction defects and/or intestinal atresia have been noted in case reports (Hoyme et al., 1990), but some of these infants were exposed to other substances. Theoretically, fetal vascular disruption could explain these malformations. Studies that include control groups are needed to determine if there is any correlation between maternal cocaine use and vascular defects.

Several retrospective studies have associated heart defects with maternal cocaine exposure during pregnancy. Lipshultz et al. (1991) found a relative risk of 3.7 (CI 1.4-9.4) for congenital heart defects in infants with a positive urine cocaine test. Little et al. (1989) studied 53 cocaine exposed infants and 100 non exposed infants, and observed cardiac defects in 4 of the exposed infants and none of the controls. However, the possibility of ascertainment bias and the reliance on self reports weaken the findings of both these studies (Holzman and Paneth, 1994).

Finally, an association with CNS accidents, such as cerebral infarcts and intraventricular hemorrhage, has been demonstrated in case reports and several small studies, and this risk may be increased in preterm infants (Chasnoff et al., 1986; Hoyme et al., 1990).

Sudden Infant Death

Several studies have reported an increased incidence of Sudden Infant Death (SIDS) with cocaine use. The increased risk may be as high as 15%, approximately 30 times that of the general population (Zuckerman et al., 1995). In contrast, a study of 175 infants exposed to cocaine and 821 controls found similar risk between the two groups (Bauchner et al., 1988). A meta-analysis found that the risk for SIDS was increased when cocaine exposed infants were compared to non-drug exposed controls, but it was not significantly increased when compared to poly-drug controls (Fares et al., 1997). Failure to account for confounding factors such as tobacco use and low socioeconomic status, which have been reported to increase the risk for SIDS, could have contributed to the high incidence of SIDS observed in some studies (Holzman and Paneth, 1994).

Neonatal Complications

Numerous studies indicate that in utero exposure to cocaine produces neonatal withdrawal. Symptoms exhibited include tremulousness, irritability, abnormal sleep patterns, poor feeding, high pitched cry and muscle rigidity (Chasnoff, 1988). These withdrawal symptoms can begin up to four days following delivery and, while transient (Holzman and Paneth, 1994), they can persist for several days to weeks (Chasnoff, 1988). Symptoms may be increased in newborns with a positive toxicology screen (Cherukuri, et al., 1988).

Several studies have assessed the neurobehavioral effects of cocaine in the immediate newborn period.

They suggest a dose-related risk for poor state regulation, attention, responsiveness, orientation and motor/tone (Delany-Black et al., 1996; Eyster et al., 1998; Hurt et al., 1995; Richardson et al., 1996). Richardson suggested that the autonomic stability and reflex changes were related to first trimester exposures, while motor maturity and tone were associated with later exposures (1996). No significant difference was seen, however, in structural brain abnormalities based on cranial ultrasound examination performed on newborns with cocaine exposure versus controls (Behnke et al., 1998). Newborns with known cocaine exposures should be closely monitored for excessive weight loss, dehydration, fever and seizures (Chasnoff et al., 1988).

Post-Natal Period

It is difficult to determine whether cocaine is a neurobehavioral teratogen. Longitudinal studies regarding development of cocaine exposed infants after the neonatal period are limited as well as difficult to interpret. One study reported that cocaine exposed infants between 6 months and 1 year scored lower in visual recognition memory (Zuckerman et al., 1995). Hurt et al. (1995) followed 101 cocaine exposed children and found no significant differences in tone, reflexes or mental development at 30 months. A follow up study on the same group found no significant differences at 4 years of age, but noted that both the cocaine exposed children and a low socio-economic control group, greater than 90% scored below the mean test score (Hurt et al., 1997). Richardson et al (1996) followed 28 children reportedly exposed to cocaine and found no difference in growth, IQ, school performance or teacher-reported behavior problems at 6 years of age. However, they noted a decrease in attention in a computer tasks. Language skills have been specifically assessed by several studies, yielding contradictory results (Hurt et al., 1997; Loebstein and Koren, 1997). A recent review of the neurobehavioral data regarding cocaine suggests that as longterm studies become available, the effects seen are more likely attributable to the social confounds and polydrug exposure (Landry and Whitney, 1996). Until additional long-term studies are completed, risks for adverse neurobehavioral outcomes following cocaine exposure in utero cannot be ascertained.

Summary:

Maternal cocaine use has been clearly associated with intrauterine growth retardation, particularly low birth weight and microcephaly, in human studies. Transient neonatal withdrawal has also been associated with in utero exposure to cocaine. Other possible associations include spontaneous abortions, malformations and SIDS. Although these risks are biologically plausible, the variability in human studies suggests a less-defined correlation with effects potentially due to dose, timing of exposure and other confounding factors. Further studies are needed to assess the long term neurobehavioral effects of cocaine use during pregnancy.

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